UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Tuesday, July 05, 2005

MEMORANDUM

Subject: Acute Toxicity Review for EPA Reg. No.: 71654-RN/ CDRW-D1
DP Barcode: D317267

To: Emily Mitchell, PM 32/ Delores Williams
Regulatory Management Branch
Antimicrobials Division (7510C)

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Applicant: E.I. DuPont de Nemours and Company

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Sodium dichloro-s-triazinetrione	45
Other Ingredient(s):	55
Total:	100.00%

1) BACKGROUND: E.I. DuPont de Nemours and Company submitted a set of four acute toxicity studies to support the registration of their new product, CRDW-D1. E.I. du Pont de Nemours and Company's Haskell[SM] Laboratory for Health and Environmental Sciences conducted these studies.

   a) This submission did not include an acute inhalation toxicity or primary eye irritation study. In addition to the four studies, this submission package includes a request to bridge acute inhalation toxicity data to support CDRW-D1. The rationales for this waiver are:

      i) The proposed product is a dry, physical blend of the registered active ingredient with other granular formulation inerts.
      ii) EPA REDs address the toxicity of both of the primary components.
      iii) Acute inhalation toxicity data already exist for a similar EPA-registered formulation (69470-23).
      iv) There is sufficient data from the formulation, its main ingredients and a similar formulation to assign precautionary labeling to this product.
      v) None of the components in the formulation is volatile (having a vapor pressure considerably less than 10^{-4} mm Hg).

   b) The registrant has also submitted a request for the waiver of the primary eye irritation study. The waiver rationales presented for this study are:

      i) The primary dermal irritation study shows this product to be a severe irritant.
      ii) Hyperkeratosis was seen in 3/3 rabbits tested.

2) RECOMMENDATIONS: PSB findings are:

   a) The acute oral toxicity, acute dermal toxicity, primary skin irritation, and, dermal sensitization studies are acceptable.

   b) CTT/PSB denies the waiver of the acute inhalation toxicity study. The reasons for the rejection are:
      i) One of the main reasons for the denial of the waiver is that the registrants cite acute toxicity data from 69470-23 to support 71654-O. The acute toxicity data requirement for 69470-23 was not satisfied through an actual acute toxicity study conducted on 69470-23. The requirement was fulfilled through the citation of other products in conjunction with waiver rationale.

ii) The registrant mentions that EPA REDs address the toxicity of the primary components of the proposed product. CTT/PSB is very concerned with the toxicity of mixtures. According to an NIH website (http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-98-002.html), "Several outcomes have been observed as a result of chemical interactions in a mixture:

(1) Chemicals act independently, and thus the chemicals in the mixture are qualitatively and quantitatively similar to their separate effects;
(2) They demonstrate additive effects, simple summing of the toxicity of the chemicals in a mixture describes the total toxicity;
(3) There are antagonistic effects, resulting in toxicity being reduced to a greater extent than would have been predicted;
(4) Chemicals demonstrate *synergism*, resulting in toxicity that is greater than additive."

In instances such as this, the registrant needs to cite a product that is highly similar in chemical formulation to the proposed product. This is called a Similarity Clinic. This cited product will have all of, or at least most of the same ingredients in the same concentrations. (CTT/PSB will also allow the registrant to bridge acute toxicity data when appropriate.) Citing several studies conducted on separate components of the product is simply not sufficient. E.I. DuPont de Nemours and Company needs to make note of this OPP/EPA policy. (This section applies to 1, (a)(i) and (ii) above.) We point out that the toxicology chapters of REDs refer to the technical active ingredients. Waivers of acute toxicity studies on technical grades of active ingredients in REDs often times do not apply to end-use mixtures or dilutions of that technical.

iii) Concerning the vapor pressure of the product and its components, EPA/OPP guidelines state:

(1) Non-volatile products are defined as those having vapor pressures <1 x 10-5 kPa (7.5 x 10-5 mmHg) for indoor uses, and <1 x 10-4 kPa (7.5 x 10-4 mmHg) for outdoor at 20-30°C.

Waiver candidates based on volatility include:

(2) A viscous liquid, gels, waxes, resins, lotions, tree injections, paints, caulks,
(3) Animal dips, shampoos, and pour-ons,
(4) Slow release collars and ear tags.

iv) The point that the proposed product is a dry, physical blend of the registered active ingredient with other granular formulation inerts is helpful information, but it is not sufficient information by itself, or with the other information submitted, to justify a waiver.

c) CTT/PSB waives the primary eye irritation study based upon the severe irritation observed in the primary skin irritation study. In accordance with the 40 CFR §158.340, this product is assigned toxicity category I for primary eye irritation. If the registrants feel that this toxicity I categorization is not representative of the hazards posed by this product, they may submit a primary eye irritation study conducted using File Symbol 71654-RN.

The acute toxicity profile for File Symbol 71654-RN is currently:

Study	MRID Number	Toxicity Category	Status
Acute Oral Toxicity	465370-01	III	Acceptable
Acute Dermal Toxicity	465370-02	IV	Acceptable
Acute Inhalation Toxicity	465370-03	?	Waiver Denied
Primary Eye Irritation	465370-04	I	Waived
Primary Skin Irritation	465370-05	II	Acceptable
Dermal Sensitization	465370-06	Sensitizer	Acceptable

3) LABELING:

a) CTT/PSB cannot recommend precautionary labeling until the registrant properly addresses the requirement for the acute inhalation toxicity study.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (§ 81-1, 870.1100)

Product Manager: 32
MRID No.: 465370-01

Reviewer: I. Blackwell
Study Completion Date: 4/26/2005
Lab Project ID.: DuPont-17269

Testing Laboratory: Haskell[SM] Laboratory for Health and Environmental Sciences
Authors: Carol Finlay, B.A.

Quality Assurance (40 CFR §160.12): Included

Test Material: CDRW-D1; "white granular solid"

Species: (female) Crl:CD®(SD)IGS BR rats
Age: 10-11 weeks
Weight: 191.5-225.0 g
Source: Charles River Laboratories, Inc.

Conclusion:

1. **LD_{50} (mg/kg):** **Males = not tested**
   Females = 976.2 mg/kg
   Combined = n/a
2. **The estimated LD_{50} is 976.2 mg/kg b.w.**
3. **Toxicity Category**: III **Classification**: Acceptable

Procedure (Deviations from §81-1):

- This study was conducted using the Up and Down Procedure. No males were tested.

Results:

Dosage (mg/kg)	(Number Deaths/Number Tested)		
	Males	Females	Combined
175	---	0/1	n/a
550	---	0/4	n/a
1,750	---	4/4	n/a
5,000	---	1/1	n/a

Observations: Clear oral discharge, low carriage, high carriage, lethargy, dark eyes, dark legs and/or paws, staining of fur and skin, wet fur, diarrhea, lack of feces, erratic breathing, prostration and moribundity.

Gross Necropsy: Discoloration of the stomach, ulceration/erosion of the stomach, red liquid in the pleural cavity, chromodacryorrhea, peritoneal adhesions in the liver, spleen, and kidneys.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2, 870.1200)

Product Manager: 32
MRID No.: 465370-02

Reviewer: I. Blackwell
Study Completion Date: 4/14/5
Lab Project ID.: DuPont-17158

Testing Laboratory: Haskell[SM] Laboratory for Health and Environmental Sciences
Author: Carol Finlay, B.A.
Quality Assurance (40 CFR §160.12): Included

Test Material: CDRW-D1; "white, granular solid"

Species: Crl:CD®(SD)IGS BR
Weight: males= 345.2-433.1g; females= 245.5-270.7g
Age: males= 11 weeks; females= 12 weeks
Source: Charles River Laboratories, Inc.

Summary:

1. **LD_{50} (mg/kg)**: **Males** > 5,000
   Females > 5,000
   Combined > 5,000

2. **The estimated LD_{50} is greater than 5,000 mg/kg b.w.**

3. **Toxicity Category**: III **Classification**: Acceptable

Procedure (Deviation From §81-2):

Results:

Reported Mortality

DOSAGE (mg/kg)	(NUMBER DEATHS/NUMBER TESTED)		
	Males	**Females**	**Combined**
5,000	0/5	0/5	0/10

Observations: Slight or mild erythema, yellow staining, scabbing, hyperkeratosis, raw areas, eschar, and/or epidermal sloughing were observed.

Gross Necropsy Findings: There was ulceration of the treated skin.

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5, 870.2500)

Product Manager: 32
MRID No.: 465370-05

Reviewer: I. Blackwell
Study Completion Date: 4/5/5
Lab Project ID.: DuPont-16936

Testing Laboratory: Haskell[SM] Laboratory for Health and Environmental Sciences
Author: Carol Finlay, B.A.

Quality Assurance (40 CFR §160.12): Included

Test Material: CDRW-D1; "white, granular solid"
Dosage: 0.5 g moistened with 0.2 mL water

Species: New Zealand White rabbits
Age: young adult
Sex: 3 males **Weight**: not reported
Source: Covance Research Products

Summary:

1. **Toxicity Category**: II
2. **Classification**: Acceptable

Procedure (Deviations From §81-5):

Results: One hour after treatment, 2/3 test animals displayed hyperkeratosis, 1/3 rough skin. Hyperkeratosis was observed in 3/3 24, 48 and 72 hours after treatment. 1/3 (animal #9) had hyperkeratosis on days 1 through 10, and had sloughing on days 6 through 10. 1/3 (#9) had well-defined erythema from 24 to 72 hours after exposure and slight edema 1 through 72 hours after exposure. 1/3 (#15) only had very slight erythema 24 through 72 hours with very slight edema 1 hour after exposure. 1/3 (#11) did not demonstrate erythema or edema during the study.

Special Comments: None.

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (§81-6, 870.2600)

Product Manager: 32
MRID No.: 465370-06

Reviewer: I. Blackwell
Study Completion Date: 4/18/5
Lab Project I.D.: DuPont-16728

Testing Laboratory: Haskell[SM] Laboratory for Health and Environmental Sciences
Author: Denise Hoban, B.A., MLT (ASCP)

Quality Assurance (40 CFR §160.12): Included

Test Material: CDRW-D1; "white granular solid"
Positive Control Material: α-hexylcinnamaldehyde in 4:1 acetone:olive oil

Species: CBA/JHsd mice
Weight: 17.5 – 22.7 grams **Age**: approx. 5 weeks
Source: Harlan Sprague Dawley, Frederick, Maryland

Method: The Local Lymph Node Assay

Summary:

1. **This Product is a dermal sensitizer.**

2. **Classification**: Acceptable

Procedure (Deviation From §81-6):
- Only females were used in this study.

Procedure Twenty-five µL of CDRW-D5 were administered topically to the dorsum of each mouse ear for 3 consecutive days (test days 0-2) at dosages of 0%, 0.006%, 0.6%, 5%, and 50%. Test days 3 and 4 were rest days followed by intravenous injection of 20 µCi of ^{3}H-Thymidine per mouse on test day 5.

Five hours after the injections, the mice were sacrificed by CO_2 asphyxiation. The draining auricular lymph nodes were removed. Then, suspensions of single cells were generated. The lab incubated these suspensions overnight at 2-8° C overnight. The counts per minute (CPM) from the cells were converted to disintegrations per minute (DPM). One mouse in the vehicle control group (#203) was classified an outlier, so its results were barred from the overall statistics.

Results:

Local Lymph Node Assay, Stimulation Index (SI)			
Test Group	Material Tested	Group Mean DPM	SI
II	0%, Vehicle Control	574.25	N/A
IV	0.006%	814.90	1.42
VI	0.6%	512.90	0.89
VIII	5%	**2447.30**	4.26
X	50%	**6293.50**	10.96
XII	Positive Control, 25%	3731.10	5.34
XIV	0% Positive Control Vehicle	698.90	N/A